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unvaccinated persons) is greater than 1, provided that systematic error (bias) and random error (sampling variation) can be shown to be improbable explanations for the findings. In other words, if a statistically significant relative risk has been obtained in an epidemiologic study (or a meta-analysis of several epidemiologic studies) and is unlikely to be due to systematic bias, *Can It?* causality can be accepted.

Much of the epidemiologic literature on causality has focused on *Can It?*, and a widely used set of criteria has evolved for *Can It?* causality assessment (Hill, 1965; Stolley, 1990; Susser, 1973; U.S. Department of Health, Education, and Welfare, 1964). These criteria are as follows:

1. *Strength of association:* A relative risk (or odds ratio) of 1.0 indicates no association between the vaccine and the adverse event. Relative risks of between 1.0 and 2.0 are generally regarded as indicating a weak association, whereas higher values indicate a moderate or strong association. In general, the higher the relative risk, the less likely the vaccine-adverse event association is to be entirely explained by one or more sources of analytic bias.

2. *Analytic bias:* Analytic bias is a systematic error in the estimate of association between the vaccine and the adverse event. It can be categorized under four types: selection bias, information bias, confounding bias, and reverse causality bias. *Selection bias* refers to the way that the sample of subjects for a study has been selected (from a source population) and retained. If the subjects in whom the vaccine-adverse event association has been analyzed differ from the source population in ways linked to *both* exposure to the vaccine *and* development of the adverse event, the resulting estimate of association will be biased. *Information bias* can result in a bias toward the null hypothesis (no association between the vaccine and the adverse event), particularly when ascertainment of either vaccine exposure or event occurrence has been sloppy; or it may create a bias away from the null hypothesis through such mechanisms as unblinding, recall bias, or unequal surveillance in vaccinated versus nonvaccinated subjects. *Confounding bias* occurs when the vaccine-adverse event association is biased as a result of a third factor that is both capable of causing the adverse event and associated with exposure to the vaccine. Finally, *reverse causality bias* can occur unless exposure to the vaccine is known to precede the adverse event.

3. *Biologic gradient (dose-response effect):* In general, *Can It?* causality is strengthened by evidence that the risk of occurrence of an outcome increases with higher doses or frequencies of exposure. In the case of vaccines, however, dose and frequency tend to be fixed. Moreover, since some of the adverse events under consideration by the committee could represent hypersensitivity or another type of idiosyncratic reaction, the absence of a dose-response effect might not constitute strong evidence against a causal relation.